OPEN ACCESS

University of BRISTOL

Van Den Brand, J. A. J. G., Pippias, M., Stel, V. S., Caskey, F. J., Collart, F., Finne, P., Heaf, J., Jais, J. P., Kramar, R., Massy, Z. A., De Meester, J., Traynor, J. P., Reisæter, A. V., Wetzels, J. F. M., & Jager, K. J. (2017). Lifetime risk of renal replacement therapy in Europe: a population-based study using data from the ERA-EDTA Registry. *Nephrology Dialysis Transplantation*, *32*(2), 348-355. https://doi.org/10.1093/ndt/gfw392

Peer reviewed version

Link to published version (if available):
10.1093/ndt/gfw392

Link to publication record in Explore Bristol Research
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via OXFORD ACADEMIC at https://academic.oup.com/ndt/article/32/2/348/2737462/Lifetime-risk-of-renal-replacement-therapy-in?searchresult=1#58953897. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/

Lifetime risk of renal replacement therapy in Europe: a population-based study using data from the ERA-EDTA Registry

Lifetime risk of RRT in Europe

Jan AJG van den Brand, [1] Maria Pippias, [2] Vianda S Stel, [2] Fergus J Caskey, [3 4] Frederic Collart,[5] Partik Finne, [6 7] James Heaf, [8] Jean-Philippe Jais,[9] Reinhard Kramar, [10] Ziad A Massy,[11 12] Johan De Meester, [13], Jamie P Traynor, [14] Anna Varberg Reisæter,[15] Jack FM Wetzels,[1] and Kitty J Jager[2]

Author affiliations:
[1]Department of nephrology, Radboud Institute of Health Science, Radboud university medical center, Nijmegen, the Netherlands.
[2]ERA-EDTA Registry, Department of Medical Informatics, Academic Medical Center, , Amsterdam, the Netherlands.
[3]Medical Director, UK Renal Registry, Southmead Hospital, Bristol, UK.
[4]Honorary Senior Lecturer, School of Social and Community Medicine, University of Bristol, UK..
[5]Nephrology and dialysis department, Brugmann Universitry Hospital, Brussels, Belgium.
[6]Department of Nephrology, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland.
[7]Finnish Registry for Kidney Diseases, Helsinki, Finland.
[8]Department of Medicine, Zealand University Hospital, Roskilde, Denmark.
[9]Université Paris Descartes, INSERM UMRS 1138 Team 22, APHP, Hôpital Necker Enfants Malades, Biostatistics Unit, Paris, France
[10]Austrian Dialysis and Transplant Registry, Rohr im Kremstal, Austria.
[11]Division of Nephrology, Ambroise Paré Univeristy Hospital, Boulogne Billancourt/Paris, France.
[12]INSERM, U-1018 Team 5 (EpReC, Renal and Cardiovascular Epidemiology), CESP, Villejeuf, France.
[13]Department of Nephrology and Dialysis and Hypertension, Dutch-Speaking Belgian Renal Registry Sint-Niklaas, Belgium.
[14]Scottish Renal Registry, Glasgow, UK.
[15]The Norwegian Renal Registry. Department of Nephrology. Department of Transplantation Medicine. Oslo University Hospital Rikshospitalet, Olso, Norway.

Correspondence to: Jan van den Brand, Department of nephrology 464, Radboud Institute of Health Science, Radboud university medical center, Geert Grooteplein Zuid 8, PO Box 9101, 6500HB, Nijmegen, the Netherlands. Telephone: +31 24 3614761. Fax +31 24 3635125. Email: jan.vandenbrand@radboudumc.nl

Word count: 3750

Keywords: End Stage Renal Disease, Renal Replacement Therapy, Mortality, Lifetime Risk, Living Kidney Donor,

Funding: European Renal Association – European Dialysis and Transplantation Association

Abstract

Background: Upcoming KDIGO guidelines for the evaluation of living kidney donors are expected to move towards a personal risk based evaluation of potential donors. We present the age and sex specific lifetime risk of renal replacement therapy (RRT) for end-stage renal disease (ESRD) in 10 European countries.

Methods: We defined lifetime risk of RRT as the cumulative incidence of RRT up to age 90. We obtained RRT incidence rates per million population by five year age groups and sex using data from the European Renal Association – European Dialysis and Transplant Association (ERA-EDTA) Registry, and used these to estimate the cumulative incidence of RRT, adjusting for competing mortality risk.

Results: Lifetime risk of RRT varied from 0.44% to 2.05% at age 20 and from 0.17% to 1.59% at age 70 across countries, and was twice as high in men as in women. Lifetime RRT risk decreased with age, ranging from an average of 0.77% to 0.44% in 20 to 70 year old women, and from 1.45% to 0.96% in 20 to 70 year old men. The lifetime risk of RRT increased slightly over the past decade; more so in men than in women. However, it appears to have stabilized or even decreased slightly in more recent years.

Conclusions: The lifetime risk of RRT decreased with age, was lower in women as compared to men of equal age and varied considerably throughout Europe. Given the substantial differences in lifetime risk of RRT between the USA and Europe, country specific estimates should be used in the evaluation and communication of the risk of RRT for potential living kidney donors.

Short summary

Recently a risk prediction model for potential kidney donors has been created for persons living in the USA. However, these estimates may not be generalizable to European populations. We provide reference values for lifetime risk of renal replacement therapy for ESRD in European countries participating in the ERA-EDTA Registry, a registry of all patients receiving renal replacement therapy (dialysis or a kidney transplant) in several countries across Europe. We showed that the risk of RRT was considerably lower in European countries compared to the USA. Moreover, we noted substantial variation in the lifetime risk of renal replacement therapy across Europe. Therefore, country specific estimates of lifetime renal replacement therapy risk should be used when evaluating a potential kidney donor.

Introduction

A living donor kidney transplant is the preferred treatment option for a patient with end-stage renal disease (ESRD). For the living donor, donating a kidney offers the potential opportunity to extend another life. However, those donating a kidney may themselves be at an increased risk of ESRD.[1] Therefore, we must ensure that those wishing to donate a kidney are adequately informed of their long-term risk of developing ESRD. Moreover, the new Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the evaluation and follow-up care of living kidney donors are expected to move towards personalized, risk based screening of potential donors. One of the likely recommendations will be that an individual may be accepted as a living kidney donor if their lifetime ESRD risk is below a certain threshold. In order to obtain a personalized lifetime ESRD risk estimate for a potential donor, one needs both a population reference for lifetime ESRD risk and information on his or her individual risk factors for ESRD. Recently the Chronic Kidney Disease (CKD) Prognosis Consortium published such a risk prediction model for the lifetime risk of ESRD in potential kidney donors.[2] This model was based on populations from Canada, the USA and Israel,[2, 3] and may not be generalizable to European populations. For example, the incidence of renal replacement therapy (RRT), defined as haemodialysis, peritoneal dialysis and kidney transplantation, in the United States is almost two times higher than that of Belgium and Greece, both countries with the highest incidence of RRT in Europe.[4, 5] Therefore, a population reference for lifetime risk of ESRD specific for European countries is required to feed any future prediction models in the European setting. To date, country specific estimates of lifetime RRT risk for Europe are lacking. In this study we present the age and sex specific lifetime risk of RRT in 10 European countries.

Subjects and Methods

Data sources and design

We performed a population based study using data obtained from the European Renal Association - European Dialysis and Transplantation Association (ERA-EDTA) Registry and publically available data from EuroStat. The primary outcome of the study was RRT for ESRD, defined as commencing chronic RRT, defined as haemodialysis, haemodiafiltration, peritoneal dialysis or pre-emptive kidney transplantation.[4] Death was considered a competing event.

The ERA-EDTA Registry

Data from twelve national or regional renal registries (Austria, Dutch-speaking Belgium, French-speaking Belgium, Denmark, Finland, France, Greece, the Netherlands, Norway, Sweden, the United Kingdom [UK]: England/Wales/Northern Ireland and the UK: Scotland), providing individual level data on patients receiving chronic RRT for ESRD to the ERA-EDTA Registry between 2002-2011 were included in the study. All registries provided data for the entire time period, with the exception of France (from 2006 onward).

Data relevant to the present study were a unique patient study number, country of registry, date of birth, sex and date of initiation of RRT. Patients commencing RRT for ESRD were included in the study. The details of the methods used by the ERA-EDTA Registry for data collection and data processing of the database can be found in the ERA-EDTA Registry annual report.[4] Informed consent was not separately obtained for the present study, as data collection was part of the routine work of the participating registries. MP used individual level data to prepare aggregated data files (included in the online supplement). JvdB performed the analyses on the aggregated data and had no access to individual level data, ensuring privacy.

Statistical methods

Incidence of renal replacement therapy by sex and age

We defined lifetime risk of RRT as the cumulative incidence of commencing RRT before age 90. We defined lifetime risk of RRT in the year 2011 as the primary outcome. The exposures of interest were

index age and sex. We defined the index age as the age that a person has reached without requiring RRT for ESRD. In addition, we assumed that the population within each country was at a steady state over the course of a year. This assumption allowed us to estimate the annual incidence rate of RRT from the incidence of RRT per million population (pmp) by five year age groups and sex for each country included in the study. [6] The incidence of RRT pmp was defined as the number of patients starting RRT annually divided by the mid-year general population within a five year age group and by sex. To minimize the effects of late reporting by the renal registries the analyses of the incidence of RRT between 2002 and 2011 were based on the ERA-EDTA Registry 2012 database.[4] The general population data and sources needed for the calculation of the incidence of RRT pmp are available from the corresponding author upon request.

Persons who are at increased risk of RRT are also at an increased risk of mortality.[7] Therefore, within survival analyses, death is a competing event, and should be accounted for when estimating the cumulative incidence of RRT.[8] Similar to the method in which we estimated the annual RRT incidence pmp, we estimated annual mortality per million of age related population (pmarp). First, we obtained the total population size and the number of deaths by five year age and sex strata for each of the participating countries from EuroStat (accessed 12th December 2014). Next, we divided the number of deaths by the total number of persons within each age and sex group. We subsequently used the incidence of RRT and mortality pmarp to estimate the number of RRT cases and deaths by five year age group and sex in the populations from which RRT incidence was obtained.

Lifetime risk of renal replacement therapy

In order to estimate the lifetime risk of RRT while taking competing mortality risk into account, we first used the number of RRT cases and deaths to estimate annual incidence rate for both RRT and death using Stata's stcompet function.[9, 10] We extrapolated the annual incidence rate according to the method described by Beiser *et al.*[11] Box 1 shows a brief description and example of this approach. We took ages 20 to 85 in five year intervals as index ages. In addition, we calculated the

ratio of the lifetime risk of RRT in women compared to men to investigate possible trends in sex specific uptake of RRT with age. Finally, we pooled the lifetime risk of RRT across Europe by calculating the inverse variance weighted mean of the country specific lifetime risk of RRT by index age. Additionally, in order to assess if possible differences in lifetime risk of RRT were due to differences in life expectancy, we checked for possible correlations between lifetime risk of RRT and life expectancy by 10 year increments of index age and by sex. We did not perform statistical significance tests for between country differences in lifetime risk of RRT. As the differences were substantial and the confidence intervals narrow, a difference greater than 0.05 percentage point would have been statistically significant.

Trends in lifetime risk of renal replacement therapy from 2002 to 2011

In order to study possible time trends in lifetime risk of RRT, we repeated the analyses for the years 2002 to 2010. In this analysis we only included the countries that provided data for the entire period from 2002 to 2011. We evaluated time trends from 2002 to 2011 using ordinary least squares regression with segments (R package segmented). First, we fitted a linear regression for women and men and index ages 20, 30, 40, 50, 60 and 70 years separately. Next we added a single knot and compared the segmented regression to the linear regression using ANOVA. If the segmented regression showed a better fit compared to the linear model another knot was added and compared to the regression with a single knot. We repeated this process until the model did not improve with the addition of further knots.

The analysis scripts that we used (Stata 11.2, StatCorp, TX, USA; and R, www.r-project.org, version 3.1.1), are available from the corresponding author upon request.

Results

Lifetime risk of renal replacement therapy by sex and age

In order to estimate the lifetime risk of RRT, we first estimated the annual incidence rate of RRT. Figure 1 shows pooled estimates of cumulative incidence of RRT by index age. The cumulative incidence of RRT increases more steeply at higher index ages compared to a low index age. However, the *lifetime* risk of RRT is higher at the lowest index ages, as illustrated in Figure 2. Men had a higher lifetime RRT risk than women across all index age groups and countries. For example, at index age 20, lifetime RRT risk varied between 0.44% (Finland) and 1.20% (Greece) for women, and between 0.88% (Finland) and 2.05% for men (Belgium). At age 40, lifetime RRT risk varied between 0.41% (Finland) and 1.17% (Greece) for women and between 0.83% (Finland) and 1.99% for men (Belgium). At age 60, lifetime RRT risk was lower still, ranging between 0.31% (Finland) and 1.05% (Greece) for women and 0.69% (Finland) and 1.83% (Belgium) for men. See the supplements for more detailed tables of lifetime risk of RRT.

Overall, the lifetime risk of RRT was approximately twice as high in men compared to women at index ages less than 65 years. However, after the age of 70, the ratio increased. At age 80 the average lifetime risk of RRT was 2.5 times as high in men and at age 85 it was three times as high in men as in women. This trend was observed in all countries except Greece, where the ratio remained stable across all age groups.

Lifetime risk of renal replacement therapy by country

The pooled lifetime RRT risk in Europe was 0.73%, 0.68% and 0.58% in 40, 50 and 60 year-old women, respectively. By comparison, in men the pooled lifetime RRT risk was 1.40%, 1.32% and 1.18% at index ages 40, 50 and 60, respectively. However, we noted variation across European countries. The lifetime RRT risks were lowest in the Scandinavian countries and the United Kingdom, and highest in Belgium and Greece. No statistically significant correlations for a possible association between lifetime risk of RRT and life expectancy were observed (data not shown). Tables with

country specific lifetime RRT risk estimates by five year increments of index age can be found in the supplementary appendix online.

Trends in lifetime renal replacement therapy risk from 2002 to 2011

Figure 3 shows pooled lifetime RRT risks in Europe between 2002 and 2011 by sex and ten year intervals of index age. Table 1 shows the trends in the lifetime risk of RRT between 2002- 2011 by sex and index age. In general, from 2002 onward lifetime RRT risk increased in both men and women. The overall increase of lifetime RRT risk was more pronounced in men, who showed a marked increase in lifetime risk of RRT until 2008 and a slight decrease in lifetime risk of RRT thereafter. Likewise, lifetime RRT risk stabilized in women after 2009. Overall, changes in lifetime risk of RRT over time were modest.

Discussion

This study describes the age and sex specific lifetime risk of RRT in 10 European countries and the average lifetime RRT risk across Europe. Even though the annual incidence rate of RRT is higher in older people compared to young people, the lifetime risk of RRT is lower in older people. In addition, lifetime risk of RRT is lower in women compared to men of the same age. We noted a substantial difference in lifetime RRT risk between countries. For instance, Belgium and Greece had a relatively high lifetime RRT risk compared to the rest of Europe, whereas the lifetime RRT risk was relatively low in Denmark, Finland, and Norway. Finally, the lifetime risk of RRT increased slightly over the past decade; more so in men than in women. However, it appears to have stabilized or even decreased slightly in recent years.

Relation to other studies

Estimates of lifetime risk of RRT have been provided previously for both the USA and Canada.[3, 12] At all ages, the lifetime risk of RRT in both the USA and Canada was two to three times as high in both men and women compared to our study. A possible explanation for the difference between the Canadian study and our study may be that persons in the Canadian study were included only if they had a serum creatinine level determined during an outpatient visit. Consequently, persons with kidney disease or co-morbidities were more likely to be included in their study sample. By using general population data we have attempted to remove this selection bias. The study from the USA, however, was a simulation study based on population data collected from the United States Renal Data System, the American registry for RRT,[12] and therefore selection bias is unlikely to explain the difference. Another possible explanation may be differences in the prevalence of risk factors for more rapid progression of CKD to ESRD. Even though the prevalence of raised blood pressure is lower in the USA and Canada compared to Europe,[13] prevalence of underlying risk factors for vascular and renal damage, such as diabetes and obesity, is higher.[14, 15] In addition, despite the majority of white Americans and Canadians being from European descent, genetic differences cannot be excluded. Finally, macro-economic factors and health system wide factors, such as the percentage of

the gross domestic product (GDP) *per capita* spent on healthcare and the proportion of dialysis centres providing RRT services for-profit may influence RRT incidence and therefore result in differences in lifetime risk of RRT between countries.[16]

Meaning of this study

We found that even though cumulative incidence of RRT increases with age, the lifetime RRT risk decreases with age. A similar trend was noted in other studies,[3, 12] and it is likely due to both competing mortality risk and conditional survival. The impact of competing mortality risk has been clearly highlighted by O'Hare and colleagues:[17] the elderly are more likely to die from competing causes, such as cardiovascular disease rather than develop ESRD. We took this competing mortality risk into account in our analyses.[8, 9] Conditional survival results in a higher probability of reaching RRT at some point *during the remainder* of one's life for younger people as they have more life years left to develop RRT.

At an index age of 65 years or less, lifetime risk of RRT in women compared to men was almost half in all countries in the present study. The reason for this difference is unclear. A recent meta-analysis showed that, at a given eGFR and albuminuria level, the risk of developing ESRD, defined as RRT, was similar for men and women with chronic kidney disease.[18] Moreover, the risk for all-cause mortality was higher in men throughout the eGFR range in general population and high risk cohorts. Therefore, the difference in RRT risk between men and women is unlikely to be explained by a competing mortality risk. In 2010, the estimated prevalence of hypertension (29.1% *versus* 21.4%) , diabetes (8.2% *versus* 7.2%), smoking (39.0% *versus* 19.3%) and high serum cholesterol (54.1% *versus* 52.7%) was higher in men than in women across Europe.[13] Differences in these risk factors between men and women may account for a substantial part of the difference in lifetime RRT risk. In addition, the decline in lifetime risk of RRT was more pronounced in women compared to men across Europe, with the exception of Greece, where this trend was not observed. It is unclear why the uptake on RRT at higher ages was lower for women compared to men.

We noted quite some variation in lifetime risk of RRT between European countries. Similar to the differences between Europe and the USA, macro-economic factors such as the GDP *per capita* and percentage of GDP spent on healthcare may contribute in differences in RRT incidence between countries within Europe.[16] In addition, differences in prevalence of risk factors such as diabetes may contribute to differences in lifetime RRT risk.[19, 20] Furthermore, some of the difference may be due to differences in medical practice.[19] For example, in a survey sent out to nephrologists in 11 European countries, 20% of the nephrologists from high RRT incidence countries reported that, even when expected gains in survival and quality of life were low, they always offer the option for RRT care compared to 8% of the nephrologists from low RRT incidence countries.[21] Finally, differences in life expectancy between countries could result in differences in RRT incidence, and thus lifetime risk of RRT. However, we did not observe an association between life expectancy and lifetime risk of RRT.

By estimating the average lifetime risk of RRT in the general population, we provide conservative estimates of the lifetime risk of ESRD. These estimates may be useful in the communication of the risk of ESRD to the general public, policy makers and individual patients. It is easier to understand percentage risk compared to other terms such as relative risks, odds ratios or hazard ratios. It should be noted, however, that the life time risk estimates that are presented here are country level averages. An individual's risk of ESRD may be far higher than the average depending on the presence of risk factors such as low eGFR, the presence of albuminuria, high blood pressure, comorbidities, and a family history of kidney disease. Such risk factors need to be taken into account when counseling individual patients.

Our results indicate that the lifetime risk of RRT in the European general population is substantially lower that the lifetime risk of RRT previously estimated for the general population in the USA.[12] The latter results were recently used as a reference level in a model predicting the lifetime risk of RRT in people who were potential kidney donors, but did not donate a kidney.[2] As the lifetime risk

in the European general population is substantially lower than in the USA, the reference level in potential living kidney donors is also likely to be lower. Consequently, the risk prediction model that was developed by the CKD Prognosis Consortium for people in the USA, Canada and Israel needs to be recalibrated and validated before implementation in Europe.

Finally, it is important to note the lifetime risk of RRT changes after kidney donation. The relative risk of RRT for ESRD is between 6 and 12 times higher in people who donated a kidney compared to equally healthy controls.[1, 22] whether this elevated risk is acceptable depends on the absolute risk of RRT for the potential donor after donation. Together with information on a potential donor's risk factors and the relative risk induced by nephrectomy, country specific reference values for lifetime risk of RRT are needed to obtain this absolute risk of RRT after kidney donation. Future studies should therefore focus on obtaining more country specific reference risk estimates for lifetime RRT before donation; only thereafter, the model by the CKD Prognosis Consortium can be validated in different national populations throughout Europe.

Strengths and weaknesses of the study

The first strong point of our study was the use of complete population survey data to obtain mortality and RRT incidence rates. Instead of taking a sample we were able to include the entire general population of each country in our analyses. In addition, the combined RRT registries provided full coverage of the population.[4] As a result, selection bias due to either sampling error or underreporting is highly unlikely. Second, in older persons the risk of mortality surpasses the risk of ESRD and subsequent RRT.[17] We took this competing mortality risk into account in our analyses.

The present study does have some limitations. First of all, the ERA-EDTA Registry does not include information on race. Therefore, we were unable to provide race stratified lifetime risk estimates. Second, lifetime RRT risk may underestimate lifetime ESRD risk. We used RRT as a proxy for ESRD, yet the two are not synonymous. Some patients, particularly those in older age groups, may opt for conservative management of ESRD, and as a result they would not be registered in national or

regional renal registries and in turn in the ERA-EDTA Registry. Nephrologists have recently estimated the proportion of new ESRD patients treated with conservative management at 10% (inter quartile range 5% to 20%).[21] Moreover, we extrapolated incidence estimates obtained from the general population to estimate annual incidence rate of RRT in persons without RRT. However, the general population includes the prevalent RRT population, *i .e*. those already receiving RRT. As RRT is relatively rare in the general population (*i.e.* less than 1 in 1000) the influence of this misclassification bias on the estimate of RRT incidence will be negligible. In conclusion, the results of our study are likely to somewhat underestimate the life time risk of ESRD especially in older age groups and therefore our results should be seen as conservative estimates for 'average' individuals. Finally, our estimates are based on historical data and for this reason they may not fully apply to future generations. However, we did not observe strong trends in lifetime RRT risk over the course of the past decade. Therefore, we feel that differences in birth cohorts will not substantially affect our estimates.

Conclusion

The present study describes the lifetime risk of RRT across Europe by sex and age group. This risk was lower in higher age groups, and it was lower in women compared to men of the same age. Given the substantial differences in lifetime risk of RRT between the USA and Europe, and between countries within Europe, country specific estimates of lifetime risk of RRT should be used when communicating risks and in the evaluation of potential living kidney donors.

Acknowledgements

We would like to thank the patients and the staff of dialysis and transplant units for contributing the data via their national and regional renal registries. We also would like to thank the following registries for the contribution of these data: Austrian Dialysis and Transplant Registry [OEDTR];Dutch speaking Belgian Society of Nephrology [NBVN] (H. Augustijn and B. De Moor); French speaking Belgian Society of Nephrology [GNFB] (JM. des Grottes); Danish Nephrology Registry [DNS]; Finnish Registry for Kidney Diseases (C. Grönhagen-Riska); The Epidemiology and Information Network in Nephrology [REIN] (M. Lassalle and C. Couchoud); Greek Renal Registry (N Afentakis); Norwegian Renal Registry (T. Leivestad); Swedish Kidney Registry [SNR] (K.G. Prütz, L. Bäckman, M. Evans, S. Schön, M. Stendahl, and B. Rippe); Nefrovisie Renine, Dutch Renal Registry (M Hemmelder and A Hemke); UK Renal Registry (All the staff of the UK Renal Registry and of the renal units submitting data); Scottish Renal Registry [SRR] (All of the Scottish renal units); In addition, we would like to thank Maurizio Nordio for providing critical revision for important intellectual content of the article, and the remaining ERA-EDTA registry committee members not mentioned above: A Więcek, JW Groothoff, J Harambat, F Jarraya, and I Rychlik; and A Kramer in the AMC Regisrty office for data collection and management.

This article was written by Jan van den Brand Maria Pippias, Vianda Stel, Fergus Caskey, Frederic Collart, Patrik Finne, James Heaf, Jean-Phillipe Jais, Reinhard Kramar, Ziad Massy, Johan De Meester, Jamie Traynor, Anna Varberg Reisæter, Jack Wetzels and Kitty Jager on behalf of the ERA-EDTA Registry which is an official body of the ERA-EDTA.

Disclosure

Competing interests: All authors declare that they have no non-financial interests that may be relevant to the submitted work.

Funding: The ERA-EDTA Registry is funded by the European Renal Association-European Dialysis and Transplant Association (ERA-EDTA).

Contributors: JvdB initiated the study, collected data, wrote the statistical analysis plan, performed the analysis, interpreted the results and drafted and revised the paper. He is guarantor. MP prepared data and performed the analysis, interpreted the results and revised the paper, VS interpreted the results and revised the paper, JW interpreted the results and revised the paper, KJ initiated the study, revised the statistical analysis plan, interpreted the results and revised the paper. The remaining co-authors provided data and revised the paper. All authors had access to the data and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency: Jan AJG van den Brand affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained. He is the guarantor for this study.

Data-sharing: The data and analysis scripts for the present study are available from the corresponding author upon request.

References

1. Muzaale AD, Massie AB, Wang MC*, et al.* Risk of end-stage renal disease following live kidney donation. JAMA 2014;311(6):579-586
2. Grams ME, Sang Y, Levey AS*, et al.* Kidney-Failure Risk Projection for the Living Kidney-Donor Candidate. N Engl J Med 2015
3. Turin TC, Tonelli M, Manns BJ*, et al.* Lifetime risk of ESRD. J Am Soc Nephrol 2012;23(9):1569-1578
4. ERA-EDTA Registry. ERA-EDTA Registry Annual Report 2012. Amsterdam, The Netherlands: Academic Medical Center, Department of Medical Informatics; 2014
5. United States Renal Data System. 2015 USRDS annual data report: Epidemiology of kidney disease in the United States. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2015.
6. Vandenbroucke JP, Pearce N. Incidence rates in dynamic populations. Int J Epidemiol 2012;41(5):1472-1479
7. Hallan SI, Matsushita K, Sang Y*, et al.* Age and association of kidney measures with mortality and end-stage renal disease. JAMA 2012;308(22):2349-2360
8. Verduijn M, Grootendorst DC, Dekker FW*, et al.* The analysis of competing events like cause-specific mortality--beware of the Kaplan-Meier method. Nephrol Dial Transplant 2011;26(1):56-61
9. Gooley TA, Leisenring W, Crowley J*, et al.* Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. Stat Med 1999;18(6):695-706
10. Choudhury JB. Non-parametric confidence interval estimation for competing risks analysis: application to contraceptive data. Stat Med 2002;21(8):1129-1144
11. Beiser A, D'Agostino RB, Seshadri S*, et al.* Computing estimates of incidence, including lifetime risk: Alzheimer's disease in the Framingham Study. The Practical Incidence Estimators (PIE) macro. Stat Med 2000;19(11-12):1495-1522
12. Grams ME, Chow EK, Segev DL*, et al.* Lifetime incidence of CKD stages 3-5 in the United States. Am J Kidney Dis 2013;62(2):245-252
13. World Health Organization. *Global Health Observatory - Blood Pressure*. http://www.who.int/gho/ncd/risk_factors/blood_pressure_prevalence/en/.
14. World Health Organization. *Noncommunicable diseases country profiles 2011*. http://www.who.int/nmh/publications/ncd_profiles2011/en/.
15. Danaei G, Finucane MM, Lu Y*, et al.* National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. Lancet 2011;378(9785):31-40
16. Caskey FJ, Kramer A, Elliott RF*, et al.* Global variation in renal replacement therapy for end-stage renal disease. Nephrol Dial Transplant 2011;26(8):2604-2610
17. O'Hare AM, Choi AI, Bertenthal D*, et al.* Age affects outcomes in chronic kidney disease. J Am Soc Nephrol 2007;18(10):2758-2765
18. Nitsch D, Grams M, Sang Y*, et al.* Associations of estimated glomerular filtration rate and albuminuria with mortality and renal failure by sex: a meta-analysis. BMJ 2013;346:f324
19. Couchoud C, Guihenneuc C, Bayer F*, et al.* Medical practice patterns and socio-economic factors may explain geographical variation of end-stage renal disease incidence. Nephrol Dial Transplant 2012;27(6):2312-2322
20. Castledine CI, Gilg JA, Rogers C*, et al.* How much of the regional variation in RRT incidence rates within the UK is explained by the health needs of the general population? Nephrol Dial Transplant 2012;27(10):3943-3950
21. van de Luijtgaarden MW, Noordzij M, van Biesen W*, et al.* Conservative care in Europe--nephrologists' experience with the decision not to start renal replacement therapy. Nephrol Dial Transplant 2013;28(10):2604-2612

22. Mjøen G, Hallan S, Hartmann A*, et al.* Long-term risks for kidney donors. Kidney Int 2014;86(1):162-167

Tables

Box 1.The estimation of lifetime RRT risk from annual RRT incidence per million population.

Lifetime risk of Renal Replacement Therapy (RRT) is the cumulative incidence of requiring RRT during the remainder of an individual's life from a certain index age at which that person was free from RRT.[3] Usually, cumulative incidence is calculated from a cohort of persons who are disease free (*i.e.* did not require RRT) at the cohort's inception, simply by dividing the number of people who have experienced an event during follow-up by the total number of persons in the cohort at its start. However, in special circumstances, namely when follow-up time is short and when an event is rare, cumulative incidence can be estimated from incidence rates.[6] Whereas cumulative incidence can only be obtained from a cohort, incidence rates per million population can be estimated from a dynamic population, such as all inhabitants of a country over the period of a year. RRT is a rare event in the general population and a single year is sufficiently short to assume that the population is in a steady state. Thus, the conditions that enable us to use annual RRT incidence rate per million population to estimate the cumulative RRT incidence are met.

Beiser *et al.* formulated an approach to extrapolate cumulative incidence to lifetime risk that takes into account survival up to a certain age – called the index age.[11] First, one-year RRT incidence rates by age strata are calculated. Next, these age specific incidence rates are used to calculate cumulative incidence for persons who have survived to a certain age, as shown in the following example:

Assume that the annual incidence rate of an event for persons aged 40 to 44 is 0.02 per 100 person years, whereas it is 0.05 per 100 person years for those aged 45 to 49. If we would have 1000 persons aged 43, how many would suffer the event by age 47?

Knowing the incidence rate, we can calculate the cumulative incidence as follows:

Age	Events	Surviving	Cumulative Incidence
43 → 44	$0.02 \cdot 1000 = 20$	980	2.0%
44 → 45	$0.02 \cdot 980 = 19.2 \approx 19$	961	3.9%
45 → 46	$0.05 \cdot 961 = 48.1 \approx 48$	913	8.7%
46 → 47	$0.05 \cdot 913 = 45.7 \approx 46$	867	13.3%

The above calculation is a simplification and not the actual calculation used in the present paper, as competing risk of death is not taken into account here. However, the approach remains conceptually similar when competing risks are accounted for. An annotated analysis script with the actual calculations is available upon request from the corresponding author.

Table 1. Trends in lifetime RRT risk between 2002 and 2011 by sex and index age.

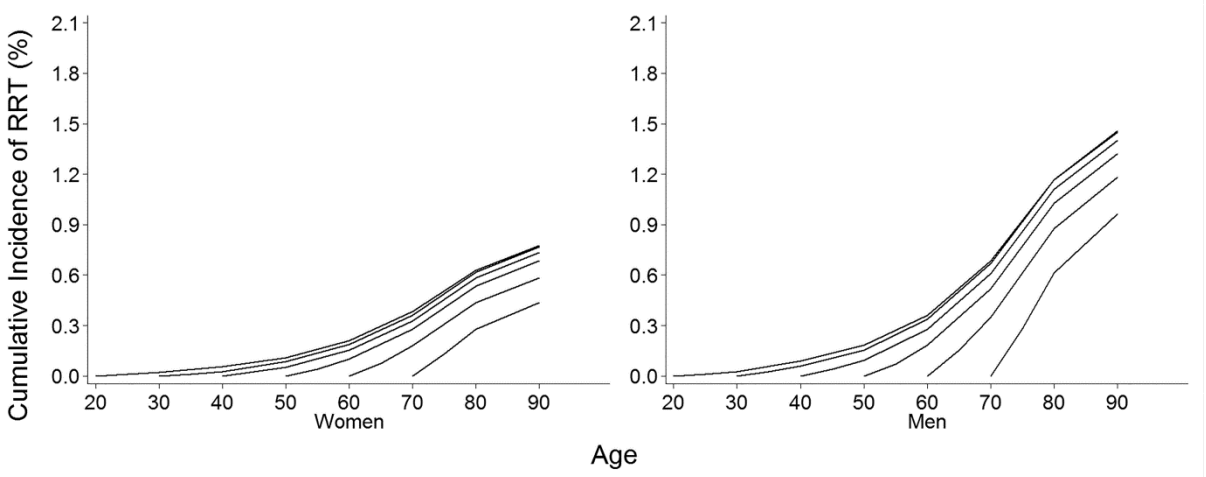
Index age	Years	Change in lifetime RRT risk per year (%)	95% Confidence interval
Women			
20	2002-2009	+0.007	0.000 - +0.014
	2010-2011	-0.026	-0.054 - +0.001
30	2002-2009	+0.007	+0.002 - +0.012
	2010-2011	-0.060	-0.107 - -0.013
40	2002-2009	+0.009	+0.003 - +0.014
	2010-2011	-0.023	-0.044 - -0.001
50	2002-2009	+0.008	+0.003 - +0.013
	2010-2011	-0.059	-0.105 - -0.013
60	2002-2009	+0.009	+0.003 - +0.014
	2010-2011	-0.023	-0.044 - -0.001
70	2002-2009	+0.008	+0.003 - +0.013
	2010-2011	-0.055	-0.101 - -0.009
Men			
20	2002-2008	+0.034	+0.025 - +0.043
	2009-2011	-0.020	-0.037 - -0.002
30	2002-2008	+0.041	+0.030 - +0.051
	2009-2011	-0.020	-0.039 - -0.001
40	2002-2008	+0.038	+0.028 - +0.048
	2009-2011	-0.017	-0.035 - +0.001
50	2002-2008	+0.038	+0.028 - +0.047
	2009-2011	-0.017	-0.035 - +0.000
60	2002-2008	+0.032	+0.022 - +0.042
	2009-2011	-0.018	-0.037 - +0.001
70	2002-2008	+0.032	+0.027 - +0.042
	2009-2011	-0.018	-0.036 - -0.000

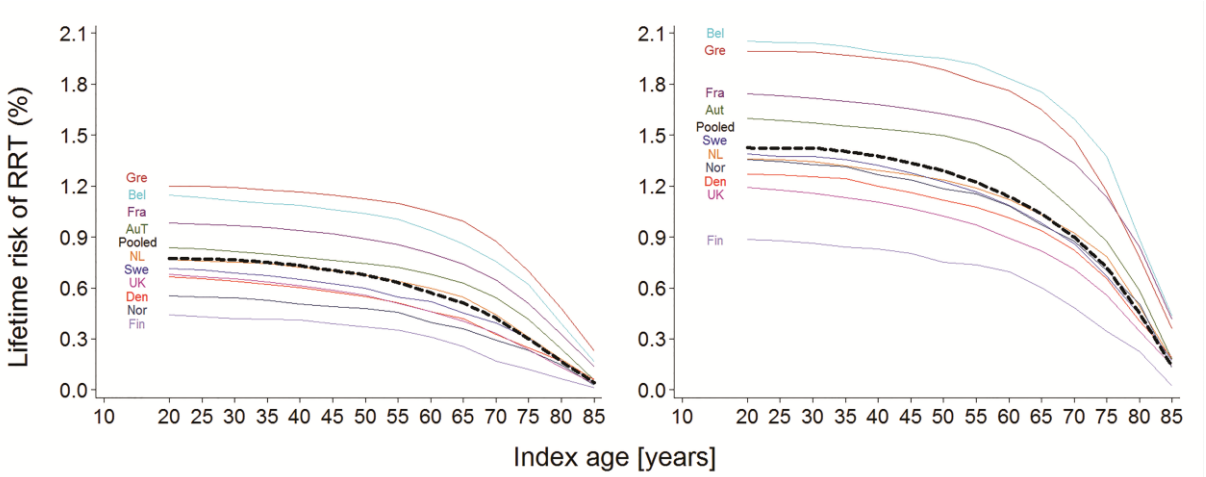
Legends to the figures

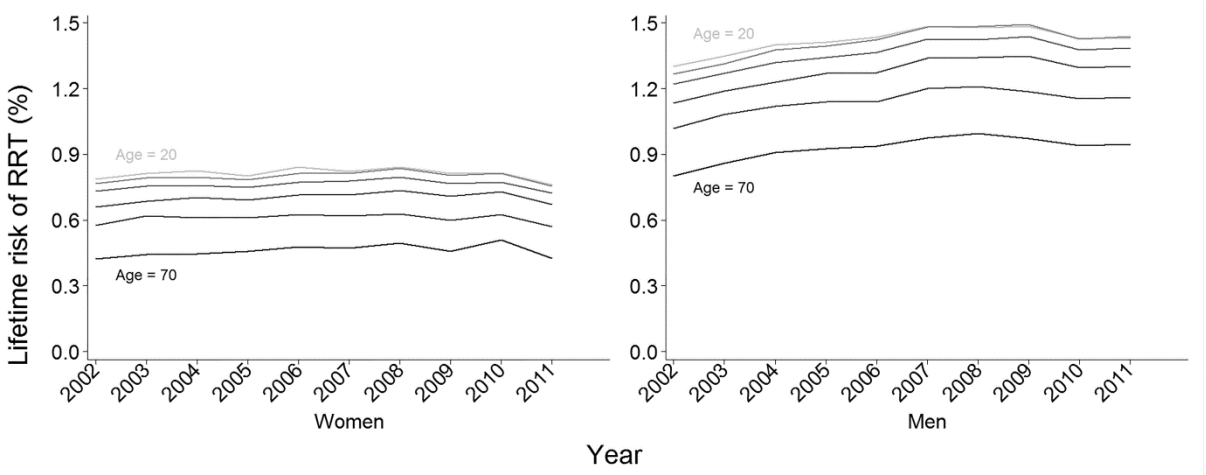
Figure 1. Cumulative incidence of renal replacement therapy in Europe by age for women (left panel) and men (right panel), respectively.

Figure 2. Lifetime risk of renal replacement therapy in Europe by index age for women (left panel) and men (right panel). The thick dotted line represents the pooled lifetime risk of renal replacement therapy. The country specific estimates are indicated by the colour coded abbreviations. Bel: Belgium, Gre: Greece, Fra: France, Aut: Austria, NL: the Netherlands, Swe: Sweden, UK: The United Kingdom, Den: Denmark, Nor: Norway, Fin: Finland.

Figure 3. Trends in lifetime risk of renal replacement therapy in Europe between 2002 and 2011 by sex at index ages 20, 30, 40, 50, 60 and 70 (from top to bottom).


Cumulative Incidence of RRT (%)
2.1
1.8
1.5
1.2
0.9
0.6
0.3
0.0
20
30
40
50
60
70
80
90
Women
Men
Age


Lifetime risk of RRT (%)
2.1
1.8
1.5
1.2
0.9
0.6
0.3
0.0
Gre
Bel
Fra
AuT
Pooled
NL
Swe
UK
Den
Nor
Fin
10 20 25 30 35 40 45 50 55 60 65 70 75 80 85
Bel
Gre
Fra
Aut
Pooled
Swe
NL
Nor
Den
UK
Fin
Index age [years]


Lifetime risk of RRT (%)
1.5
1.2
0.9
0.6
0.3
0.0
Age = 20
Age = 70
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
Women
Men
Year

Copyright

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0.

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, a worldwide licence to the Publishers and its licensees in perpetuity, in all forms, formats and media (whether known now or created in the future), to i) publish, reproduce, distribute, display and store the Contribution, ii) translate the Contribution into other languages, create adaptations, reprints, include within collections and create summaries, extracts and/or, abstracts of the Contribution, iii) create any other derivative work(s) based on the Contribution, iv) to exploit all subsidiary rights in the Contribution, v) the inclusion of electronic links from the Contribution to third party material where-ever it may be located; and, vi) licence any third party to do any or all of the above.